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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOSEPH ROBERTS and NATARAJAN SETHURAMAN

Appeal 2010-010365
Application 09/972,245
Technology Center 1600

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-6, 11-13, 17-22, 41, 42, and 44, directed to a method of protecting therapeutic compositions from host-mediated inactivation. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

"When a host encounters a foreign agent in its circulation, the host's immune system may initiate an immune response. This response includes the production of agent-inactivating antibodies that also enable the reticuloendothelial system to clear the agent from circulation" (Spec. 1: 7-9).

"One strategy for protecting these agents is to covalently modify them with agents like carbohydrates or biocompatible polymers, like Polyethylene Glycol ('PEG')" (*id.* at 1: 15-16). "PEGylation increases the stability of proteins . . . and also greatly reduces their antigenicity (measured by the extent of reaction of antibodies raised against unmodified protein to PEGylated protein) and immunogenicity (measured by the extent of antibody formation against PEGylated protein in treated animals), as measured by *in vitro* immunological techniques" (*id.* at 1: 19 to 2: 1).

One drawback of this protection is that "PEGylation often reduces the biological activity of the agent. The extent of reduction varies with the type of activated PEG used and the number of Polyethylene Glycol moieties attached to the agent. The biological activity also is affected by the extent to which an agent is modified with a particular PEG" (*id.* at 2: 3-7).

According to Appellants, choosing modification conditions for a given therapeutic agent (i.e., the type of activated PEG to use, and the extent of modification) based only on the criteria of initial "acceptable loss of therapeutic activity . . . and the reduction of antigenicity and immunogenicity of the agent" (*id.* at 2: 8-11) "often leads to an arbitrary result" (Spec. 1: 12-13), and is "insufficient . . . where such agents are administered . . . over a prolonged period of time" (*id.* at 2: 17-19).

According to Appellants, this is "because none of the foregoing criteria take into consideration the effect of the host's response on the agent's biological activity *after* the PEGylated agent is administered to the host" (*id.* at 2: 19-21). "[O]ver-PEGylation of an agent, as well as over-modification of an agent with any modifying agent, can disrupt the secondary and/or tertiary structure of the agent, thus exposing new antigenic determinants to the immune system" (*id.* at 3: 4-6).

According to Appellants, measuring the loss of therapeutic activity of the modified agent before it is administered to a patient is not relevant to predicting subsequent host-mediated loss of activity (*id.* at 2: 8 to 3:8). Nor is the extent of antibody formation against the modified agent (i.e., antigenicity and immunogenicity) "predictive of clearance of activity" (*id.* at 27: 4). Thus, "reliance on only the aforementioned criteria will produce an agent that is not optimally protected from the host's immune system, or otherwise from *in situ* inactivation" (*id.* at 2: 21-23).

The Specification describes "a direct *in vivo* functional method of ascertaining modification conditions of a therapeutic agent that allow the agent to evade the host's self-defense mechanisms and consequently extend the effective therapeutic life of the therapeutic agent in the host" (*id.* at 5: 12-15).

STATEMENT OF THE CASE

> The basic inventive method entails administering a modified therapeutic agent . . . to a subject. Next, the blood of the subject is assayed for biological activity of the therapeutic. The subject is then treated with one or more doses of the modified agent . . . at levels useful in therapy. The blood of the subject is assayed again for biological activity of the therapeutic agent . . . Any decrease in activity from the first measurement

> and subsequent measurements is ascertained. The foregoing may be repeated multiple times. The method may also be repeated with different lots of therapeutic agent, which differ in the extent of modification. An ideal level of modification is that which yields the smallest decrease in biological activity between doses.

(Spec. 21: 7-15.)

Claims 1-6, 11-13, 17-22, 41, 42, and 44 are pending and on appeal.

Claims 1 and 17 are representative:

1. A method for determining the type of biocompatible polymer, the extent of the modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

17. A method of preparing a pharmaceutical composition where host-mediated inactivation is prevented, comprising selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected.

Claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Boos,[1] Kawashima,[2] Ettinger,[3] Saito,[4] and Francis.[5]

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[1] J. Boos et al., *Monitoring of Asparaginase Activity and Asparagine Levels in Children on Different Asparaginase Preparations*, 32A EUROPEAN JOURNAL OF CANCER 1544-1550 (1996).

[2] Kohei Kawashima et al., *High Efficiency of Monomethoxypolyethylene Glycol-Conjugated L-Asparaginase (PEG_2-ASP) in Two Patients with Hematological Malignancies*, 15 LEUKEMIA RESEARCH 525-530 (1991).

[3] Lawrence J. Ettinger, *An Open-Label, Multicenter Study of Polyethylene Glycol-L-Asparaginase for the Treatment of Acute Lymphoblastic Leukemia*, 75 CANCER 1176-1181 (1995).

[4] Tetsuya Saito et al., *Chemical Modification of L-Asparaginase with Comb-Shaped Copolymer of Poly(ethylene glycol) Derivative and Maleic Anhydride*, 11 LEUKEMIA 408-409 (1997).

[5] G.E. Francis et al., *PEGylation of Cytokines and Other Therapeutic Proteins and Peptides; the Importance of Biological Optimisation of*

Claim 4 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Pedersen.[6]

Claims 8, 11, and 20-22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Abuchowski.[7]

Claim 19 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Bollin, Jr.[8]

OBVIOUSNESS

Findings of Fact

1. Boos describes a monitoring program in which children being treated for acute lymphoblastic leukemia and non-Hodgkin's lymphoma received induction and re-induction therapy with one of two different unmodified asparaginases derived from *Escherichia coli*, or an asparaginase derived from *Erwinia chrysantemi* when allergic reactions to the *E. coli* enzymes were observed (Boos 1545, col. 1).

2. Asparaginase activity, "the primary parameter of this drug monitoring" (Boos 1545, col. 1), was measured and compared in blood samples collected before each of eight asparaginase infusions, which were applied at 3-day interverals (*id.* at 1545, col. 1-2; Figs. 2-5). "Additional pharmacodynamics parameters measured included asparagine levels, as the

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Coupling Techniques, 68 INTERNATIONAL JOURNAL OF HEMATOLOGY 1-18 (1998).

6 Pedersen et al., US 6,531,122 B1, March 11, 2003.

7 Abraham Abuchowski et al., *Treatment of L5178Y Tumor-Bearing BDF$_1$ Mice with a Nonimmunogenic L-Glutaminase-L-Asparaginase*, 63 CANCER TREAT. REP. 1127-1132 (1979).

8 Bollin, Jr. et al., US 4,678,812, July 7, 1987.

main biochemical parameter of the desired therapeutic effect, and the aspartic acid concentration and levels of glutamine and glutamic acid, as parameters potentially associated with toxic side-effects" (*id.* at 1545, col. 1).

3. According to Boos, although each type of asparaginase has different chemical and immunological properties, "preparations are usually interchanged without modifying the dosage or the application interval" (Boos 1545, col. 1). After evaluating their performance *in vivo*, however, Boos concluded that the "pharmacological differences between different asparaginase preparations need to be translated into corresponding dosage recommendations. The logical consequence will be to opt for specification of the particular preparation to be used for all treatment protocols employing asparaginase" (*id.* at 1549, col. 1).

4. Kawashima discloses monomethoxypolyethylene glycol-conjugated L-asparaginase (PEG_2-ASP). According to Kawashima, PEG_2-ASP has a number of advantages over unmodified asparaginase, notably, "extremely high anti-tumor activity in mice with spontaneous lymphoma, it does not react with anti-L-ASP antibodies nor does it induce the synthesis of new antibodies against L-ASP *in vivo*" (Kawashima 525).

Multiple doses of the PEG_2-ASP were administered to patients with hematological malignancies over an extended period of time (Kawashima 526, col. 2). "Blood samples were drawn . . . at different time intervals during the PEG_2-ASP treatment" and "[e]nzyme activity was determined by measuring L-aspartate formation." (*id.* at 526, col. 1). The asparagine content of the sera was analyzed as well (*id.*).

5. Ettinger describes a Phase II clinical trial to characterize the efficacy and toxicity of PEG-L-asparaginase in patients with acute lymphoblastic leukemia (Ettinger 1176). According to Ettinger, "PEG-L-asparaginase is potentially less immunogenic compared with native L-asparaginase" (*id.* at 1179), and "[t]he toxicity of PEG-L-asparaginase compared favorably with . . . native L-asparaginase when administered during induction therapy with vincristine, prednisone, and doxorubicin" (*id.* at 1180). Ettinger also determined that "[s]erum asparagine levels were undetectable for up to 26 days in patients who received PEG-L-asparaginase" (*id.* at 1179).

6. Saito teaches that L-asparaginase modified with a comb-shaped copolymer of a polyethylene glycol derivative and maleic anhydride, PM-asparaginase, "lost its immunoreactivity with retention of its enzymatic activity" (Saito 408). Moreover, in comparison with PEG_2-asparaginases, "PM-asparaginase reduced the immunoreactivities at lower degrees of modification than PEG_2-modified ones and retained high enzymatic activities" (*id.*).

7. According to the present Specification, "the terms subject, patient and animal are used interchangeably. Suitable subjects . . . include mammals, in particular rodents . . . and humans. In a preferred embodiment, the subject is a human" (Spec. 14: 4-7).

Discussion

All four of the rejections are based in whole or in part on the Examiner's proposed combination of Boos, Kawashima, Ettinger, Saito, and Francis, so we will discuss the rejections together. Appellants have waived

any arguments based on the other references cited by the Examiner (*see* Appeal Br. 15-16).

We agree with the Examiner that the claimed invention would have been obvious over the cited prior art. That is, we agree with the Examiner that it would have been obvious to monitor and compare the activities of two or more enzymes, modified to different extents with different biocompatible polymers (e.g., Kawashima's PEG_2-ASP, Ettinger's PEG-L-asparaginase, and Saito's PM-asparaginase), after administering multiple doses to patients, in order "to determine which one was more active over the course of treatment because it is in the best interest of future patients to do so" and because "activity correlates with therapeutic effect" (Ans. 10). Stated another way, we agree that it would have been obvious to compare differently-modified asparaginases and select one that maintains its enzymatic activity over the course of therapy (e.g., Kawashima's PEG_2-ASP), especially as the prior art indicates that asparaginases are generally administered frequently, over a long period of time (FF2).

Appellants contend that "<u>the cited references either compare two unmodified asparaginases or one modified and one unmodified asparaginase</u>, and not two modified therapeutic agents, as recited in (a) - (e) of the appealed claims" (Reply Br. 12). Appellants contend that "the prior art would not have identified which type of biocompatible polymer, the extent of modification and the conditions for modification to prevent host-mediated inactivation" (*id.*), "because only one type of biocompatible polymer, if any, was used in each of the prior-art comparison steps" (*id.*), and "because <u>the art does not teach a step in which these specific modification variables are compared and then selected</u>" (*id.*). Appellants contend that the prior art

methods "only identify in absolute terms which therapeutic agent . . . yielded a greater therapeutic benefit, and do not ascertain information regarding the modification features relevant to preventing host-mediated inactivation" (*id.* at 13).

This argument is not persuasive. We agree with the Examiner that the prior art provides ample reason for one of skill in the art to choose a modified asparainase over an unmodified one, and also provides evidence that several differently-modified asparaginases were known in the art. As for comparing and selecting modification variables, Saito teaches that PM-asparaginase reduced the immunoreactivity of unmodified asparaginase at lower degrees of modification than PEG_2-modified ones and still retained high enzymatic activities (Saito 408; FF6). It would have been obvious for one skilled in the art to compare differently-modified asparaginases and select one with modifications that allow it to maintain its catalytic activity over the course of treatment, because that would provide the greatest therapeutic benefit.

Appellants contend that the Examiner "seeks to transform the claimed invention from its developmental setting of optimizing the modification of a therapeutic enzyme to that of the clinical setting, where the therapeutic benefit of candidate compounds is assessed" (App. Br. 12). Appellants contend that the Examiner has ignored clause (e) of claim 1 and the preamble of the claim, which mandate that "the claimed invention is a therapeutic optimization scheme" (Reply Br. 13) that "occurs in the preclinical context" (*id.* at 14). Appellants contend that "identification of the type of biocompatible polymer, the extent of modification, and conditions for modification for a therapeutic agent [to prevent host-mediated

inactivation] could only occur before the modified therapeutic is selected for use in a clinical setting" (*id.* at 13). Appellants contend that "the therapeutic candidates in the art have been selected already, regardless of their ability to prevent host-mediated inactivation" (*id.* at 14). Appellants contend that "one of [their] insights was to abandon convention and optimize the modification [of] a therapeutic enzyme by evaluating, after *in vivo* administration, the modified enzyme's capacity to catalyze its reaction" (App. Br. 11-12), and "[n]othing in the cited materials . . . suggests that such testing should be applied in the preclinical setting of research and development" (*id.* at 11).

We are not persuaded. First, we disagree with Appellants that the preamble, or anything in the body of the claim, restricts the claimed method to a particular environment, or imposes a temporal limitation on the claimed method. That is, we see nothing in the preamble or the body of the claim that distinguishes between a "clinical setting" and a "preclinical" or "developmental setting," especially as the claims explicitly require administering the modified enzymes to humans (*see e.g.,* claim 41, which defines the immunocompetent subject as a "person"). Nor do we find anything in the preamble or body of the claims that requires steps (a) through (e) to "occur before the modified enzyme is selected for use in a clinical setting" (Reply Br. 14). Nor, for that matter, have Appellants identified anything in the Specification that imposes such limitations on the claims.

Second, to the extent Appellants contend that the claimed invention is directed to selecting modifications which will allow the enzyme to evade inactivation *in vivo*, while the prior art focuses on therapeutic efficacy of

modified enzymes that have already been selected for use in a clinical setting without regard to identifying modifications that will prevent inactivation, we do not agree that this amounts to a patentable distinction. Appellants contend essentially that the claims require preparing a series of modified enzymes; administering the modified enzymes to different subjects at least twice; and identifying those modified enzymes that resist host-mediated inactivation (i.e., identifying those modified enzymes that remain active after more than one administration), for *subsequent* production (e.g., as in claim 17) and clinical evaluation of therapeutic efficacy. Appellants contrast this with "[t]he prior art, [which] measures asparaginase biological activity in the context of a treatment protocol . . . and compares the candidates to identify which one had a greater therapeutic effect" (Reply Br. 14). Appellants emphasize that "the therapeutic candidates in the art have been selected already, regardless of their ability to prevent host-mediated inactivation" (*id.*).

The problem here is that the therapeutic benefit of unmodified or modified asparaginase *is* its ability to catalyze its reaction - enzyme activity and therapeutic benefit are one and the same in this case. Again, we agree with the Examiner that the prior art provides ample reason for one of skill in the art to choose a modified asparainase over an unmodified one, and also provides evidence that several differently-modified asparaginases were known in the art. It would have been obvious for one skilled in the art to compare them and select one with modifications that allow it to maintain its catalytic activity over the course of treatment, because that would provide the greatest therapeutic benefit. Whether that selection occurs before or

after some other selection process is a circumstance that is simply not captured by the claims.

SUMMARY

The rejection of claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis is affirmed.

The rejection of claim 4 under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Pedersen is affirmed.

The rejection of claims 8, 11, and 20-22 under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Abuchowski is affirmed.

The rejection of claim 19 under 35 U.S.C. § 103(a) as unpatentable over Boos, Kawashima, Ettinger, Saito, Francis, and Bolin is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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